Table 3. Summary of Malignant Tumors for Male Mice from Study MC3536 on Tomoxetine (Compound 139603)

Site - Neoplasm	Total Incidence	Dose Group 00 (n=60)	01 (n=60)	02 (n=60)	03 (n=60)	Peto's Trend Test Z	one-sided P-value
Liver - Hepatocellular Carcinoma	28	9	10	6	3	-1.787	0.963
Lung - Alveolar/Bronchiolar Carcinoma	17	6	6	5	0	-2.044	0.980
Whole Animal - Lymphosarcoma	12	3	5	1	3	-0.461	0.678
Spleen - Hemangiosarcoma	4	1	3	0	0	-1.303	0.904
Liver - Hemangiosarcoma	4	1	2	1	0	-0.844	0.801
Whole Animal - Histiocytic Sarcoma	4	1	1	2	0	-0.413	0.660
Skin - Fibrosarcoma	3	2	0	0	1	-0.695	0.756
Liver - Cholangiocarcinoma	2	0	2	0	0		
Accessory Ocular - Adenocarcinoma	2	0	0	1	1		
Skeletal Muscle - Hemangiosarcoma	1	0	1	0	0		
Duodenum - Adenocarcinoma	1	0	0	1	0		
Skeletal Muscle - Rhabdomyosarcoma	1	0	0	1	0		
Skeletal Muscle - Fibrosarcoma	1	0	0	0	1		
Eye - Adenocarcinoma	1	0	0	0	1		

Table 4. Summary of Benign Tumors for Male Mice from Study MC3536 on Tomoxetine (Compound 139603)

Site - Neoplasm	Total Incidence	Dose Group 00 (n=60)	01 (n=60)	02 (n=60)	03 (n=60)	Peto's Trend Test Z	one-sided P-value
Lung - Alveolar/Bronchiolar Adenoma	18	6	5	4	3	-1.088	0.862
Liver - Hepatocellular Adenoma	12	5	3	4	0	-1.819	0.966
Accessory Ocular - Adenoma	10	2	2	4	2	-1.095	0.863
Skin - Papilloma	3	1	2	0	0	-1.316	0.906
Adrenal - Pheochromocytoma	3	0	3	0	0	-0.733	0.768
Pancreas - Islet Cell Adenoma	2	0	2	0	0		
Adrenal - Adenoma	2	0	2	0	0		
Skin - Fibroma	2	0	0	0	2		
Urinary Bladder - Transitional Cell Papilloma	1	1	0	0	0		
Testis - Interstitial Cell Tumor	1	1	0	0	0		
Prostate - Papilloma	1	1	0	0	0		
Skin - Trichoepithelioma	1	1	0	0	0		
Urinary Bladder - Hemangioma	1	0	1	0	0		
Skin - Hemangioma	1	0	1	0	0		

Table 5. Summary of Malignant Tumors for Female Mice from Study MC3536 on Tomoxetine (Compound 139603)

Site - Neoplasm	Total Incidence	Dose Group 00 (n=60)	01 (n=60)	02 (n=60)	03 (n=60)	Peto's Trend Test Z	one-sided P-value
Whole Animal - Lymphosarcoma	32	7	7	8	10	0.601	0.274
Whole Animal - Histiocytic Sarcoma	11	3	4	3	1	-1.061	0.856
Skin - Fibrosarcoma	5	2	2	1	0	-1.457	0.927
Lung - Alveolar/Bronchiolar Carcinoma	4	2	2	0	0	-1.873	0.969
Spleen - Hemangiosarcoma	3	2	0	0	1	-0.835	0.798
Skeletal Muscle - Hemangiosarcoma	3	2	0	0	1	-0.833	0.798
Skeletal Muscle - Rhabdomyosarcoma	2	2	0	0	0		
Bone - Osteosarcoma	2	1	0	0	1		
Ovary - Fibrosarcoma	2	1	0	1	0		
Skeletal Muscle - Fibrosarcoma	2	1	0	1	0		
Mammary Gland - Adenocarcinoma	2	0	1	0	1		
Liver - Hepatocellular Carcinoma	2	0	0	1	1		
Liver - Hemangiosarcoma	1	1	0	0	0		
Lung - Fibrosarcoma	1	1	0	0	0		
Pancreas - Fibrosarcoma	1	1	0	0	0		
Uterus - Endometrial Stromal Sarcoma	1	1	0	0	0		
Accessory Ocular - Carcinoma, Undifferentiated	1	1	0	0	0		
Diaphragm - Fibrosarcoma	1	1	0	0	0		
Adrenal - Fibrosarcoma	1	1	0	0	0		
Kidney - Osteosarcoma	1	0	1	0	0		
Lung - Osteosarcoma	1	0	1	0	0		
Lymph Node - Osteosarcoma	1	0	1	0	0		
Salivary Gland - Adenocarcinoma	1	0	1	0	0		
Skeletal Muscle - Osteosarcoma	1	0	1	0	0		
Mass 1 - Osteosarcoma	1	0	1	0	0		
Mesentery - Fibrosarcoma	1	0	0	1	0		
Ovary - Papillary Cystadenocarcinoma	1	0	0	1	0		
Skin - Hemangiosarcoma	1	0	0	0	1		

Table 6. Summary of Benign Tumors for Female Mice from Study MC3536 on Tomoxetine (Compound 139603)

Site - Neoplasm	Total Incidence	Dose Group 00 (n=60)	01 (n=60)	02 (n=60)	03 (n=60)	Peto's Trend Test Z	one-sided P-value
Accessory Ocular - Adenoma	9	2	5	0	2	0.817	0.207
Pituitary - Adenoma	8	5	1	1	1	-1.974	0.976
Lung - Alveolar/Bronchiolar Adenoma	6	2	3	0	1	-1.234	0.891
Adrenal - Pheochromocytoma	4	1	2	0	1	-0.555	0.710
Liver - Hepatocellular Adenoma	3	1	1	1	0	-0.845	0.801
Pylorus - Adenoma	2	1	0	1	0		
Urinary Bladder - Transitional Cell Papilloma	1	1	0	0	0		
Ovary - Cystadenoma	1	1	0	0	0		
Skin - Hemangioma	1	1	0	0	0		
Pancreas - Cystadenoma	1	0	1	0	0		
Ovary - Papillary Cystadenoma	1	0	1	0	0		
Uterus - Hemangioma	1	0	1	0	0		
Skin - Fibroma	1	0	1	0	0		
Skin - Keratoacanthoma	1	0	1	0	0		
Ovary - Granulosa-Theca Tumor, Benign	1	0	0	1	0		
Uterus - Leiomyoma	1	0	0	1	0		
Bone - Osteoma	1	0	0	0	1		
Thyroid - Follicular Cell Adenoma	1	0	0	0	1		

Toxicokinetics: not available from this study. Toxicology report 34 (study # M01098) entitled: "A blood level study in B6C3F1 mice administered tomoxetine hydrochloride (LY139603) in the diet for 3 months" included in the submission studied blood levels. The study was done in 1998. Mice (4/sex in the control group, 44/sex in the treated groups) received diets containing 0.0, 0.025, 0.1, and 0.4% tomoxetine (lot # 3999SB7)

comparison to the control group. The sponsor negated a drug effect on mortality since at study termination the effect was only seen in one of the replicate studies and not the other. This early mortality observation was not seen in the F. Decreases in both bdwt and bdwt gain were observed in both M and F at the MD and HD and they were seen at an earlier time at the HD. Minor increases in leukocytes were observed in M at all doses. No drug effects were observed on clinical chemistry parameters. Changes on organ wts were observed but contradicting findings in the replicate studies made it difficult to pinpoint a definitive drug effect. Consistent findings in both replicate studies were seen as a decrease in the absolute wt of liver in both M and F at the HD. Gross pathology changes such as whole tissue alteration was seen in the liver and spleen of F treated with the drug and not the control. Overall there were no clear neoplastic changes.

Adequacy of the carcinogenicity study and appropriateness of the test model: there were few observations about the conduct of these studies, which prompted some attention to their appropriateness.

1) For example the fact that there were two separate studies done was unusual for these studies and might bring some complications to data handling at the statistical level. There seems to be no major variability in the data obtained from these studies except for some occasional contradictions in the findings of the replicate studies in regard to organ wts. This was not generally observed in all other parameters measured and in general the variability seen in the two studies did not show more variability than what one might observe in a single study between the individual animals.
2) The fact that drug exposure was calculated based on the amount of food consumed by the historical control and not the animals in the studies was of major concern. It would have been more appropriate to measure the amount of food consumed by the animals in the study and then calculate the amount of drug that these animals have consumed. This is important because if the drug affects food consumption in mice, which was the subject of another study conducted later 1988 (study # M00687, ToxRep #26), then the calculated values in this study are irrelevant. In study # M00687, mice (3/cage) were treated with drug (0.3% in mash feed) for up to 51/2 months. Food consumption was measured during weeks 3, 4, 7, 8, 11, 12, 15, 16, 19, 20, 23, and 24 of study as total food consumed by all 3 mice in one week divided by the number of mice/cage and by the length of the time to give amounts as g/mouse/day. The results of the study demonstrated that a decrease in food intake is seen in mice (see tables 6.1-6.2 provided by sponsor). In females, food consumption at the end of the period was decreased by 12% in comparison to the control group, and in males the decrease was 7%.

TABLE 6.1. AVERAGE DAILY FOOD CONSUMPTION OF MALE B6C3F$_1$ MICE FED DIETS CONTAINING TOMOXETINE FOR FIVE AND ONE-HALF MONTHS. STUDY M00687

		Average Food Intake (g/mouse/day)		
		Animals/Cage		
Week	Dose Group	1	2	3
3	Control			3.83
	Treated	4.39	3.25	3.25
4	Control			4.15
	Treated	4.84	4.23	3.80
7	Control			4.16
	Treated	4.34	3.74	3.78
8	Control			4.64
	Treated	4.57	4.22	4.21
11	Control		[a] ___	4.29
	Treated	3.68		3.75
12	Control			4.70
	Treated	4.97	4.36	4.42
15	Control	6.07		4.71
	Treated	4.86	4.57	4.45
16	Control	5.70		4.68
	Treated	4.75	4.40	4.30
19	Control	5.68		4.67
	Treated	5.03	4.62	4.79
20	Control	5.77		4.74
	Treated	4.70	4.33	4.44
23	Control	6.11		4.72
	Treated	5.28	4.56	4.42
24	Control	6.09		4.65
	Treated	4.58	4.18	4.32

[a] Spilled feed wet. Unable to weigh accurately.

TABLE 6.2. AVERAGE DAILY FOOD CONSUMPTION OF FEMALE B6C3F$_1$ MICE FED DIETS CONTAINING TOMOXETINE FOR FIVE AND ONE-HALF MONTHS. STUDY M00687

		Average Food Intake (g/mouse/day) Animals/Cage	
Week	Dose Group	2	3
3	Control		3.53
	Treated		2.98
4	Control		3.90
	Treated		3.33
7	Control		3.67
	Treated		3.19
8	Control		3.98
	Treated		3.73
11	Control		3.57
	Treated		3.29
12	Control		4.83
	Treated		3.94
15	Control		4.28
	Treated		4.29
16	Control		4.43
	Treated		4.08
19	Control		4.46
	Treated		3.98
20	Control		4.38
	Treated	4.14	4.14
23	Control		4.35
	Treated	4.79	3.86
24	Control		4.48
	Treated	3.74	3.94

If the results of this later study can be used to recalculate the exposure levels of the animals in the 2-year carcinogenicity study, then the exposure levels will be less than what is proposed. Therefore, males' exposure level will be 401 mg/kg/day instead of the 436 and the females' exposure will be 421.5 mg/kg/day instead of 479. These new recalculated values are termed "corrected doses" (see adequacy of carcinogenicity section later).

3) No toxicokinetic studies were performed to measure drug levels in this study, which could have been helpful especially to compare these levels to those in humans. However, a study conducted in 1998 measured blood drug levels in

TABLE 1. TEST ARTICLE PURITY VALUES OF COMPOUND LY139603. STUDIES R11282 AND R11382.

Assay Date	Lot Number	Purity (percent)
September 15, 1981*	866-83F-248	98.3
July 28, 1982	866-83F-248	100.0
January 27, 1983	866-83F-248	99.51
September 15, 1981*	866-83F-250	97.3
January 18, 1984	866-83F-250	101.0
September 15, 1981*	866-83F-249	98.9
June 5, 1984	866-83F-249	99.69
July 17, 1984	866-83F-249	100.3
October 31, 1984	866-83F-249	99.5

*Original test article characterization value.

CAC concurrence: see addendum at the end

Study Type: 2-year bioassay
Species/strain: rat, Fischer 344
Number/sex/group, age at start of study: 60 (30 from each study)/sex/dose, 5-6 wks old
Animal housing: animals were individually housed in metal cages. Animals from the two studies were housed in two different rooms and were from two different shipments; however, according to the sponsor they were similar in all other aspects (supplier, strain, and experimental protocol).
Formulation/vehicle: the test article was administered to the rats in a mash feed containing 0, 0.01, 0.03 or 0.1% tomoxetine.
Drugs stability/homogeneity: diets were prepared every two weeks and stored at room temperature. Test article distribution (homogeneity) and stability in the feed was determined. The measured values for the homogeneity of the test article in the feed were within 10% of the theoretical value. The content of the test article in the feed, which was measured at different times during the study length, was near the theoretical levels and it

appeared to be stable in the feed for up to 4-weeks. For the stability of the test article itself with time see the previous table under drug lot # and purity.

Methods:

Doses: dietary concentrations of 0.0, 0.01, 0.03, or 0.1% which provided time-weighted average daily doses of 0.0, 4.2, 12.7, or 42.5 mg/kg for M and 0.0, 5.2, 15.4, or 51.3 mg/kg for F.

Basis of dose selection: according to the sponsor, dose selection was based on a previous three-month subchronic toxicity study since "this study indicated definite treatment related effects at the middle and high-dose levels". A description of these effects was not provided. However, according to the sponsor's summary of the three month study and according to the summary table of data, a decrease of up to ~7% in body wt of males and up to 9% in females was observed. The sponsor indicated that "the choice of the high dose of 0.1% in the diet as the maximum tolerated dose (MTD) follows the dose selection criteria as defined in the Office of Science and Technology Policy document on chemical carcinogenesis" (Federal Register vol. 50 (50) chapter 3, pp 10411-10420, March 14, 1985).

According to the sponsor, doses used here represent approximately 5, 15, and 50 times the human dose. The proposed human dose is up to 1.8 mg/kg/day, therefore the doses used here represent 2.9, 8.6, and 28.5 times the human dose which is less than what the sponsor has indicated.

Restriction paradigm of dietary restriction studies: no restrictions

Route of administration: dietary

Frequency of drug administration: ad libitum daily for two years

Dual controls employed: one control group was used for each replicate study

Interim sacrifices: no interim sacrifice

Satellite PK or special study group(s): none

Deviations from original study protocol: these studies were completed in 1984, however, they were reopened in 1998 in order to conduct further statistical analysis (tumor incidence was analyzed statistically after the data were adjusted for survival and Peto's test was conducted).

Statistical methods: see the previous section.

Observations and times:

Clinical signs: animals were examined daily for general physical condition and behavior. A detailed examination that included muscle tone, condition of pelage, color and appearance of eyes, respiration, posture, excreta, locomotion, and the presence of external lesions or growths, was performed weekly.

Body weights: body weight was examined weekly

Food consumption: food consumption and efficiency of food utilization (body weight gained in g/100 g of food consumed) were evaluated weekly.

Hematology: at termination with animals fasted overnight, blood was collected via cardiac puncture. Parameters evaluated were erythrocyte count, hemoglobin, packed cell volume, total and differential leukocyte counts, erythrocyte morphology, mean cell volume, mean cell hemoglobin, and mean cell hemoglobin concentration.

Clinical Chemistry: at study termination. Parameters evaluated: glucose, urea nitrogen, creatinine, total bilirubin, alkaline phosphatase, and alanine transaminase.

Organ weights: during necropsy the weight of the following organs were evaluated: adrenals, brain, heart, kidneys, liver, ovaries, prostate, spleen, testes, thyroids, and uterus. Relative organ weights (to body and brain wts) were calculated.

Gross pathology: at necropsy a systematic gross examination of general physical condition, body orifices, external and internal organs and tissues was conducted for each animal.

Histopathology: histopathological preparations of the following organs were performed during necropsy: kidney, liver, heart, lung, spleen, thymus, lymph node, salivary gland, pancreas, stomach, duodenum, jejunum, ileum, colon, ovary, uterus, adrenal, thyroid, testis, prostate, skin, mammary gland, skeletal muscle, urinary bladder, bone, bone marrow, eye, cerebrum, cerebellum, brain stem, pituitary, and gross lesions.

Toxicokinetics: not performed.

Results

Mortality: there was no increase in mortality rate in treated animals as opposed to control animals. The mortality rate in animals of both studies was comparable during the reported weeks (starting week 43 in males and week 37 in females). The overall survival rates of combined studies at two years were 68.3, 58.3, 65.0, and 66.7% for males and 63.3, 75.0, 76.7, and 78.3% for females receiving 0.0, 0.01, 0.03, and 0.1% tomoxetine, respectively. The following table summarizes survival levels at the end of the 24 months.

APPEARS THIS WAY
ON ORIGINAL

TABLE 5. SURVIVAL DATA OF RATS GIVEN LY139603 IN THE DIET FOR TWO YEARS. STUDIES R11282 AND R11382.

Dose (% in Diet)	Number of Survivors at 24 Months			Total Percent Survival
	R11282	R11382	Total	
		MALES		
0.0	18	23	41	68.3
0.01	18	17	35	58.3
0.03	21	18	39	65.0
0.1	22	18	40	66.7
		FEMALES		
0.0	21	17	38	63.3
0.01	25	20	45	75.0
0.03	22	24	46	76.7
0.1	25	22	47	78.3

Overall Survival for Both Sexes	Total	Total Percent
0.0	79	65.8
0.01	80	66.7
0.03	86	70.8
0.1	87	72.5

Clinical signs: one of the clinical observations that was found to be higher in treated males was the incidence of lose stool which was increased 26% at all doses in comparison to control group. This increase was not seen in females who however exhibited higher levels of chromodacryorrhea in response to treatment (31/60 in control,

35/60 in LD, 42/60 in MD, and 39/60 in HD group). Ventral soiling was increased in both males and females with treatment (3/60 in control, 11/60 in LD, 7/60 in MD, and 16/60 in HD males, 10/60 in control, 22/60 in LD, 30/60 in MD, and 30/60 in HD females). The incidence of "eyes filmed over" was increased in males (1/60 in control, 1/60 in the LD, 2/60 in the MD and 4/60 in the HD). This observation was comparable between the treated and control groups in females. The incidence of "whole animal pale" was dose dependently higher in treated females in comparison to controls (5/60 in control, 6/60 at LD, 11/60 at MD, and 13/60 at HD). Females also exhibited arched backs in response to treatment that was more obvious at the HD (3/60 in controls, 4/60 in LD, 6/60 in MD, and 19/60 in HD). This was not seen in any of the males. The sponsor associated this observation to the significant body weight loss in females of this group (HD).

Body weights: a decrease in body wt (5%) in the HD males was statistically different from controls, according to the sponsor's statistical analysis starting day 42 and continued throughout the study. A comparable decrease in body wt was seen at MD, however it was not statistically significant according to the sponsor's statistical analysis. Near the end of the study the LD males experienced a slight decrease in body wt (~3%) that was not consistently statistically significant. Females experienced a decrease in body wt (~3%) at HD around day 21 and this decrease was up to 10-15% later in the study. Females treated with MD also experienced a decrease in body wt (~3%) that was seen around day 42 and was statistically significant according to the sponsor's statistical analysis. Towards the end of the study the decrease at MD was up to ~7%. A decrease in body wt (~3%) was also seen in females at LD which started around day 55 and continued throughout the study even though it was not statistically significant at all reported times. Changes in wt gain were comparable to changes in body wt for both males and females. See the following two figures for changes in body wt with time in both males and females.

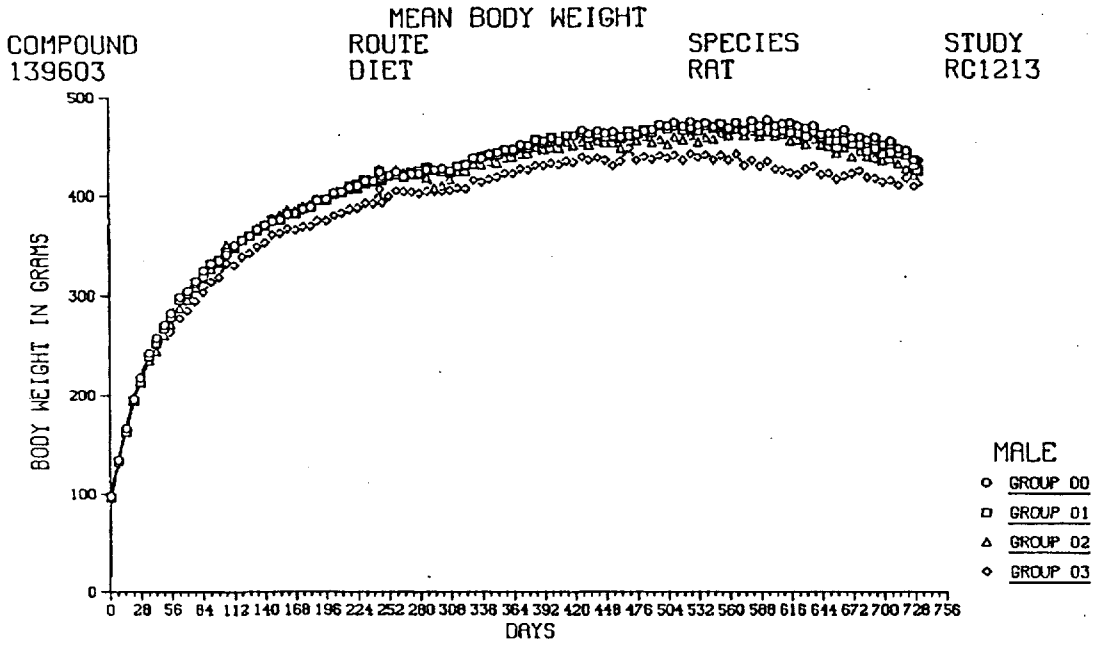
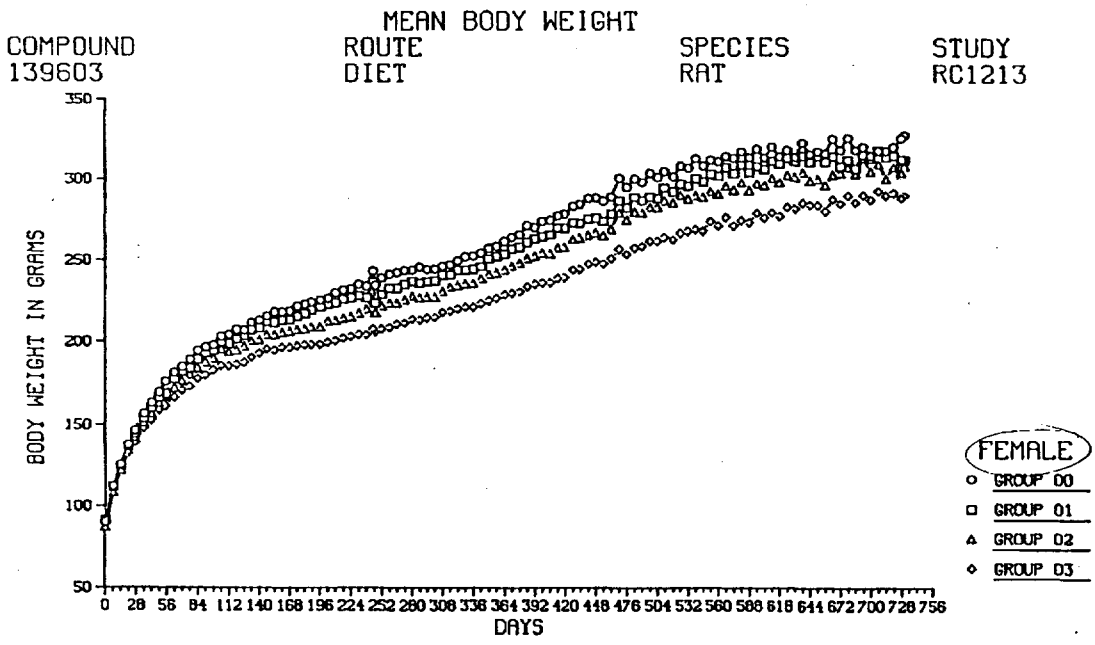

MEAN BODY WEIGHT
COMPOUND
139603
ROUTE
DIET
SPECIES
RAT
STUDY
RC1213
BODY WEIGHT IN GRAMS
500
400
300
200
100
0
0 28 56 84 112 140 168 196 224 252 280 308 336 364 392 420 448 476 504 532 560 588 616 644 672 700 728 756
DAYS
MALE
GROUP 00
GROUP 01
GROUP 02
GROUP 03

FIGURE 3.2


MEAN BODY WEIGHT
COMPOUND
139603
ROUTE
DIET
SPECIES
RAT
STUDY
RC1213
BODY WEIGHT IN GRAMS
350
300
250
200
150
100
50
0 28 56 84 112 140 168 196 224 252 280 308 336 364 392 420 448 476 504 532 560 588 616 644 672 700 728 756
DAYS
FEMALE
GROUP 00
GROUP 01
GROUP 02
GROUP 03

Food consumption: food consumption was reduced (6-10% compared to the control, combined studies) in males treated with HD from the beginning to the end of the study. A decrease in food consumption (~3%) was seen at the MD at the beginning (up to week 14) which was statistically significant according to the sponsor's statistical analysis. Food consumption in males treated with LD was not different from the control. Females experienced decreases in food consumption of 5% at LD, 11% at MD and 13% at HD compared to control and this decrease lasted throughout the study. See the following table for a summary of food consumption in the two studies at termination.

TABLE 9. SUMMARY OF GROWTH FOR RATS GIVEN LY139603 IN THE DIET FOR TWO YEARS. STUDIES R11282 AND R11382.

Dose (% in Diet)	Mean Weight At Start (g)	Number of Survivors	Mean Weight At Termination (g)	Mean Weight Gain (g)	Mean Daily Food Consumption (g)	Mean E.F.U.[a]	Mean Daily Intake of LY139603 (mg/kg/day)
Study R11282							
				MALES			
0.0	90.6	18	443.2	353.2	16.6	2.9	--
0.01	89.6	18	431.1	340.9	16.6	2.8	4.20
0.03	91.7	21	420.5	329.1	16.3	2.8	12.80
0.1	89.1	22	406.8	316.4	15.8[b]	2.7	42.83
				FEMALES			
0.0	85.2	21	329.4	245.9	12.9	2.6	--
0.01	88.2	25	315.6	227.7	12.5	2.5	5.21
0.03	82.6	22	300.5	219.7	12.1[b]	2.5	15.50
0.1	82.8	25	290.2[c]	207.3[c]	11.5[b]	2.4	52.02
Study R11382							
				MALES			
0.0	105.1	23	426.0	322.5	16.5	2.7	--
0.01	103.2	17	416.1	309.4	16.6	2.6	4.17
0.03	103.0	18	425.4	319.2	16.7	2.6	12.61
0.1	101.3	18	414.9	318.4	15.9[c]	2.7	42.14
				FEMALES			
0.0	94.3	17	325.3	231.5	12.8	2.5	--
0.01	93.9	20	307.0	214.5	12.5	2.3	5.09
0.03	91.3	25	315.1	224.0	12.1[b]	2.5	15.19
0.1	91.2	22	289.5[c]	198.0[c]	11.4[b]	2.4	50.53

[a]E.F.U. = Efficiency of food utilization - grams of body weight gained per 100 grams of food consumed.

[b]Significantly different from control, $p \leq 0.01$, Dunnett's two-tailed "t".

[c]Significantly different from control, $p \leq 0.05$, Dunnett's two-tailed "t".

Efficiency of food utilization defined as grams of body wt gained /100 g of food consumed was calculated and tended to be reduced in both males and females at HD.
Test article intake was reduced with time at all doses in both males and females as depicted in figures provided by the sponsor (Figures 9.1 and 9.2). The following table prepared by the reviewer summarizes the calculated time-weighted average daily dose of tomoxetine and the calculated weekly range of average daily doses from the combined studies. The higher values in the range were observed at the beginning of the study and the lower values were observed towards the end of the study.

		Calculated time-weighted average daily dose of tomoxetine (mg/kg/day)	**Calculated weekly range of average daily doses of tomoxetine (mg/kg/day)**
Sex	**Group**		
M	LD	4.2	3.19 – 10.43
	MD	12.7	9.59 – 30.1
	HD	42.5	33.79 – 98.86
F	LD	5.2	3.71 – 10.1
	MD	15.4	11.28 – 29.26
	HD	51.3	39.45 – 95.46

FIGURE 9.1

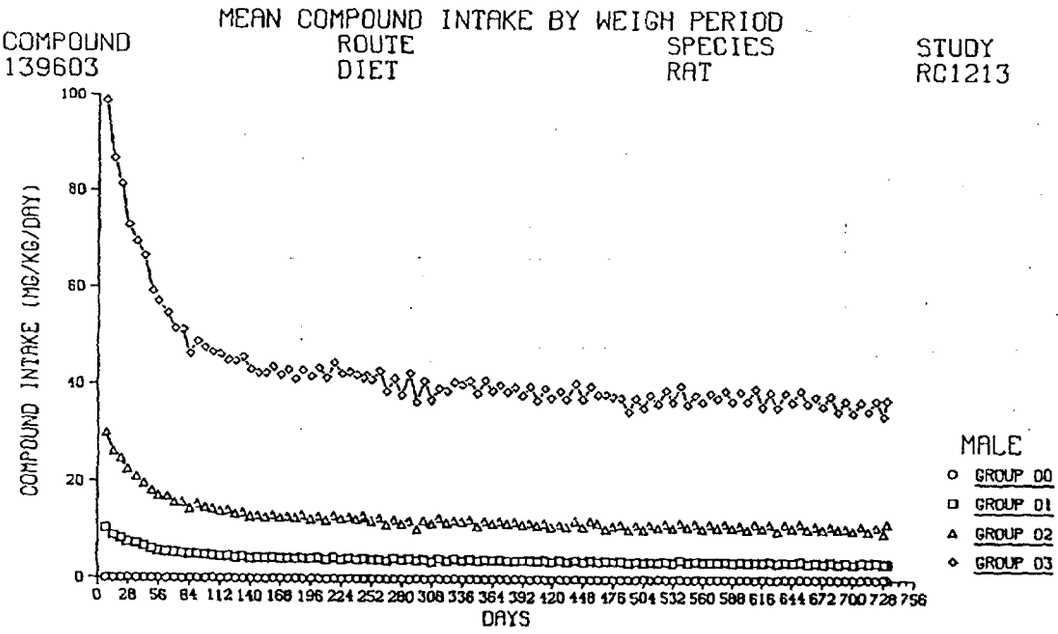
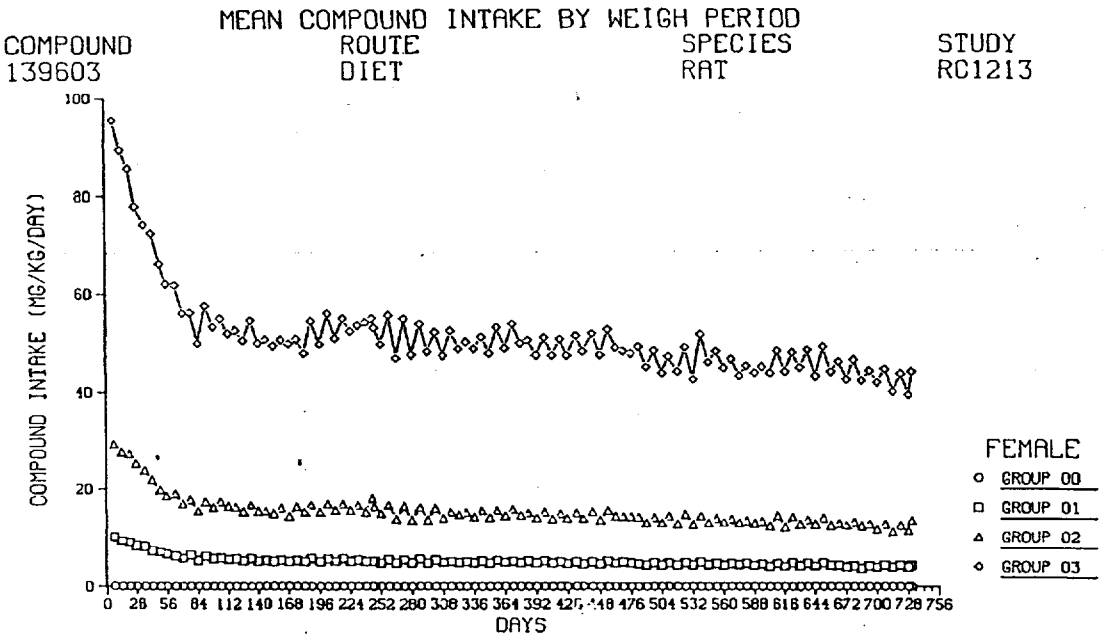


FIGURE 9.2



Hematology: some discrepancies were observed between the two studies in regard to some of the hematological parameters measured. For example an increase in erythrocytes, Hgb and PVC was observed in males with all doses in study R11382 while a decrease in these parameters was observed in study R11282, therefore, in the combined results there was no effect observed. No differences in these parameters were observed in females. Decreases in lymphocytes (11-30%) were observed in males at MD and HD in both studies and an increase (135%) in females at HD in study R11282 and a decrease (62%) at MD and (56%) at HD in study R11382.

Clinical Chemistry: an increase in glucose levels (~13%) was seen at MD and HD in males which was consistent in both studies while females did not show this increase. An increase (~20%) in BUN was observed at all doses in males in the combined studies with no discrepancies between the two studies, and an increase of a lesser extent (~11%) was seen in females at the MD and HD which was mainly seen in study R11282.
Increases in creatinine (20-26%) were observed in males at LD and MD but not HD in the combined studies and only at the LD (~20%) in females.

Organ weights: no major changes were seen in either males or females and sometimes contradicting findings were reported between the two studies and some of the findings were not dose-related.

Gross pathology: some changes in the liver referred to by the sponsor as "lesion" were observed when the studies were combined in males where 2/60 were reported for

the control group, 7/60 in the LD, 7/60 in the MD, and 6/60 in HD. Nodules in the mesentery tended to be higher at MD dose in both males and females. In the combined studies, nodules in the mesentery in males were 6/60 in control and 9/60 in MD, while in females there were 5/60 in control and 9/60 at MD. In the combined studies, the number of enlarged testes was higher than control only at MD (4/60 in control and 7/60 at MD).

Histopathology:

Non-neoplastic: the incidence of moderate progressive glomerulonephrosis was increased in both males and females in the combined studies. The incidence in males was 18/60 in controls, 15/60 in LD, 29/60 in MD, and 32/60 in HD while the incidence in females was 6/60 in controls, 16/60 in LD, 14/60 in MD, and 12/60 in HD. The incidence of severe progressive glomerulonephrosis in males was also increased with treatment in the combined studies where 2/60 were observed in the control, 8/60 in LD, 9/60 in MD and 6/60 in HD.

In the combined studies, severe diffuse vacuolation in the liver was observed in females only in the LD and HD groups (0/60 in control, 3/60 at LD, and 2/60 at HD). In addition, minimal multiple vacuolation was increased in treated females compared to the controls (8/60 in controls, 6/60 at LD, 14/60 at MD, and 11/60 at HD). Slight multiple vacuolation was also increased in treated females in comparison to controls (9/60 in controls, 15/60 in LD, 17/60 in MD, and 11/60 in HD). Moderate multiple vacuolation was increased in males treated with drug in comparison to controls (1/60 in control, 7/60 in LD, 9/60 in MD, and 17/60 in HD). Severe multiple vacuolation was observed in LD (2/60) and HD (1/60) males and LD (1/60) females and none in the control groups.

Diffuse atrophy (acini) in the pancreas seemed to increase with treatment in males (2/60 in controls, 7/60 in LD, 6/60 in MD and 8/60 in HD).

Some level of parasitic change was seen in the colon of males in response to treatment (9/60 in control, 12/60 in LD, 14/60 in MD, and 12/60 in HD) in the combined studies.

Slightly higher incidence of focal hyperplasia in the cortex of the adrenal in females in the combined studies (3/60 in control, 3/60 in LD, 4/60 in MD, and 5/60 in HD). Increased incidence of diffuse vacuolation in the cortex of the adrenal in females with treatment (3/60 in control, 6/60 at LD, 5/60 at MD, and 5/60 at HD).

Thyroid C-cell adenomas appear to increase in females at the HD (10/60 in comparison to control 5/60).

Pituitary cysts were seen in the treated groups and not in the control in males (0/60 in control, 2/60 in LD, 2/60 in MD, and 3/60 in HD groups). Pituitary focal hyperplasia was somewhat increased with treatment in males (2/60 in control, 7/60 at LD, 3/60 at MD, and 4/60 at HD), while in females the incidence was higher than the control only at the HD (4/60 in controls, 4/60 at LD, 4/60 at MD, and 7/60 at HD).

The incidence of unilateral cataracts appeared to increase with dose in males and only at HD in females. The incidence in males was 0/60 in control, 2/60 at LD, 3/60 at MD, and 5/60 at HD and in females the incidence was 3/60 in control and 5/60 at HD. The incidence of bilateral cataracts appeared to change with treatment only in males (0/60 in control, 1/60 in LD, 5/60 at MD, and 2/60 at HD). When the total number of animals with cataracts (males and females with both unilateral and bilateral cataracts) were combined the incidence was higher in the treated groups (6/120 in controls, 7/120 in LD, 9/120 in MD, and 12/120 in HD).

Neoplastic:

Benign tumors: a high incidence of interstitial cell tumor in the testes was observed in both control and treated males equally. Skin fibroma occurrence was higher in males at HD (3/60 in the control, 2/6 at LD, 1/60 at MD, and 6/60 in the HD). Thyroid C-cell adenoma occurrence was higher at HD in females (5/60 in control, 5/60 at LD, 2/60 at MD, and 10/60 at HD). Adrenal pheochromocytoma occurrence was higher in females at HD (1/60 in control, 0/60 at LD, 2/60 in MD, and 3/60 in HD). The incidence of fibroadenoma of the mammary gland in females appeared to decline with treatment (13/60 in controls, 11/60 in LD, 4/60 in MD, and 5/60 in HD). The following two tables summarize the list of benign tumors in both males and females.

Table 4. Summary of Benign Tumors for Male Rats from Study RC1213 on Tomoxetine (Compound 139603)

		Dose Group				Peto's Trend Test	
Site - Neoplasm	Total Incidence	00 (n=60)	01 (n=60)	02 (n=60)	03 (n=60)	Z	one-sided P-value
Testis - Interstitial Cell Tumor	197	50	50	48	49	0.512	0.696
Pituitary - Adenoma	71	23	15	18	15	-1.292	0.902
Thyroid - C-Cell Adenoma	21	6	4	4	7	0.295	0.384
Adrenal - Pheochromocytoma	20	8	5	4	3	-1.643	0.950
Pancreas - Islet Cell Adenoma	19	4	5	7	3	-0.164	0.565
Skin - Fibroma	12	3	2	1	6	0.968	0.167
Skin - Keratoacanthoma	8	2	2	4	0	-0.691	0.755
Skin - Lipoma	4	1	2	1	0	-0.969	0.834
Liver - Hepatocellular Adenoma	3	0	2	1	0	-0.255	0.601
Skin - Trichoepithelioma	2	1	1	0	0		
Mammary Gland - Fibroadenoma	2	1	0	0	1		
Skin - Basal Cell Epithelioma	2	1	0	1	0		
Skin - Adenoma	2	0	1	1	0		
Mammary Gland - Adenoma	1	1	0	0	0		
Skeletal Muscle - Lipoma	1	1	0	0	0		
Parathyroid - Adenoma	1	1	0	0	0		
Cerebrum - Astrocytoma, Benign	1	1	0	0	0		
Skin - Neurofibroma	1	0	1	0	0		
Bone - Osteoma	1	0	1	0	0		
Lips - Papilloma	1	0	0	1	0		

Table 6. Summary of Benign Tumors for Female Rats from Study RC1213 on Tomoxetine (Compound 139603)

		Dose Group				Peto's Trend Test	
Site - Neoplasm	Total Incidence	00 (n=60)	01 (n=60)	02 (n=60)	03 (n=60)	Z	one-sided P-value
Pituitary - Adenoma	92	28	21	23	20	-1.676	0.953
Mammary Gland - Fibroadenoma	33	13	11	4	5	-2.871	0.998
Thyroid - C-Cell Adenoma	22	5	5	2	10	1.042	0.149
Pancreas - Islet Cell Adenoma	6	1	1	3	1	0.312	0.378
Adrenal - Pheochromocytoma	6	1	0	2	3	1.372	0.085
Uterus - Hemangioma	4	2	1	1	0	-1.363	0.914
Skin - Fibroma	4	2	0	1	1	-0.597	0.725
Mammary Gland - Adenoma	4	0	2	2	0	-0.105	0.542
Uterus - Leiomyoma	4	0	0	3	1	1.276	0.101
Ovary - Granulosa-Theca Tumor, Benign	3	1	2	0	0	-1.441	0.925
Skin - Adenoma	3	0	1	2	0	0.146	0.442
Skin - Neurofibroma	2	1	1	0	0		
Brain Stem - Astrocytoma, Benign	2	0	0	0	2		
Liver - Hepatocellular Adenoma	1	1	0	0	0		
Cervix - Lipoma	1	1	0	0	0		
Adrenal - Ganglioneuroma	1	1	0	0	0		
Meninges - Osteoma	1	1	0	0	0		
Skin - Lipoma	1	0	1	0	0		
Mammary Gland - Cystadenoma	1	0	1	0	0		
Meninges - Lipoma	1	0	1	0	0		
Lung - Alveolar/Bronchiolar Adenoma	1	0	0	1	0		
Uterus - Adenoma	1	0	0	1	0		
Uterus - Cystadenoma	1	0	0	1	0		
Uterus - Fibroma	1	0	0	1	0		
Adrenal - Adenoma	1	0	0	1	0		

Malignant tumors: the incidence of mononuclear cell leukemia in males and females was decreased in drug treated groups in comparison to control (the incidence in males was 19/60 in control, 21/60 in LD, 11/60 in MD, and 12/60 in HD and in females the incidence was 15/60 in control, 12/60 in LD, 5/60 in MD, and 9/60 in HD). Whole animal lymphosarcomas were seen in HD treated females (0/60 in control and 3/60 at HD). A summary of malignant tumors in males and females are summarized in the following tables.

(LY139603) in the diet for 3 months" was performed in 1998 to measure blood levels in a comparable paradigm. Rats (5/sex/control group, 18/sex/treatment group) received tomoxetine HCl at a concentration of 0.0, 0.01, 0.03, and 0.1% in the diet for 3 months. These dietary levels provided average daily tomoxetine HCl doses of 0.0, 7.2, 21.4, or 69.2 mg/kg for males and 0.0, 8.1, 23.6, or 74.7 mg/kg for females. Plasma concentration of tomoxetine and its metabolites (4-hydroxytomoxetine and N-desmethyltomoxetine) were determined in blood samples collected from 3 animals/sex/treatment on days 5, 35, and 90 at different time points (0, 4, 8, 12, 16, and 20 hours on Days 5 and 90 and on Day 35 at Hour 4). There is an increase in the levels of tomoxetine in response to the dose, no gender effect and continued exposure resulted in decreased plasma concentrations of tomoxetine over time in males (a reduction of 35-45% in AUC by Day 90). The following table summarizes these results.

		Male			Female		
	Tomoxetine HCl	Study Day of Sample Collection					
Parameter[a]	in Feed	Day 5	Day 35[b]	Day 90	Day 5	Day 35[b]	Day 90
AUC (ng•hr/mL)	**0.01%**	102.7	NA	63.8	89.5	NA	80.2
C_{max} (ng/mL)		6.6	4.7	4.1	5.3	3.4	5.4
C_{min} (ng/mL)		3.4	NA	1.4	2.8	NA	2.0
AUC (ng•hr/mL)	**0.03%**	299	NA	195	246	NA	236
C_{max} (ng/mL)		17.9	14.4	11.5	15.8	13.0	15.4
C_{min} (ng/mL)		10.0	NA	5.7	7.3	NA	5.8
AUC (ng•hr/mL)	**0.1%**	1199	NA	665	913	NA	852
C_{max} (ng/mL)		81.9	115	43.8	52.4	23.9	50.2
C_{min} (ng/mL)		36.2	NA	15.8	29.2	NA	20.3

[a] Results are reported as tomoxetine free base.

[b] Result of single sample point taken from 3 rats at 8 p.m.

AUC (Area Under the Curve) = AUC of tomoxetine from 4 p.m. to 12 p.m. the following day (20 hrs).

NA = Not applicable since only a single sample point was taken.

Summary of individual study findings: two replicate studies, 2-weeks apart, were conducted with 30 rats/sex/group for each study. The drug was administered orally in a mash feed containing 0.0, 0.01, 0.03, or 0.1% tomoxetine. These values provided time-weighted average daily doses of 0.0, 4.2, 12.7, or 42.5 mg/kg for M and 0.0, 5.2, 15.4, or 51.3 mg/kg for F. The study lasted two years and animals were examined daily for general physical condition and weekly for a more detailed exam. Body weights and food consumption were evaluated weekly. Hematology and clinical chemistry were performed at the end of the study and gross pathology and histopathology were performed at necropsy. There was no increase in mortality rate in response to treatment. Lose stool was increased in males at all doses and ventral soiling was increased in both males and females with treatment. The incidence of "eyes filmed over" was higher than the control

at HD in males. Females tended to have curved backs with treatment but was more pronounced at the HD. The sponsor related this finding to the loss in body wt that the females experienced at this dose. A slight decrease in body wt in males in comparison to control was seen at HD. Females experienced a decrease in body wt compared to control at HD and to a lesser extent at MD and LD. In the combined studies, a decrease in food consumption was seen at MD (up to week 14) and HD (throughout the study length) in males and at all doses (throughout the study) in females. Hematological changes were insignificant and some discrepancies between the two studies were noted. An increase in glucose levels was seen at MD and HD in males only. An increase in BUN was seen at all doses in males and at MD and HD in females. Grossly, "lesions" in the liver were observed in males at all doses. Histopathology indicated increased incidences of glomerulonephrosis (moderate progressive in both males and females, severe progressive in males only). Vacuolation in the liver, which was described as diffuse and multiple, was observed in both males and females with different levels of severity. Increased incidence of cataracts in males and females especially at HD. Some incidence of some benign tumors was found to be higher with treatment such as skin fibroma in males at HD and thyroid C-cell adenoma in females at HD. The incidence of fibroadenoma of the mammary gland in females appeared to decline with treatment. The incidence of mononuclear cell leukemia in males and females was decreased in drug treated groups.

Adequacy of the carcinogenicity study and appropriateness of the test model:

1) Some of the concerns about this study are similar to those discussed in the mouse study:
2) Two studies were performed with two batches of animals in different rooms evaluated on different times (studies were conducted two weeks apart), however, the sponsor indicated that everything else was similar.
3) Drug levels in the feed was constant and was not adjusted for the decrease in food intake, therefore, as was obvious, animals were exposed to higher levels of the drug at the beginning of the study in comparison to those at the end of the study.
4) Toxicokinetic data were obtained in a separate study performed many years later.

Evaluation of tumor findings: as is obvious from the summary table of the malignant and benign tumors reported here, there does not appear to be a concern of an increase in tumor incidence in response to drug treatment. There were two tumor categories that decreased in their incidence in response to drug treatment, namely the malignant mononuclear cell leukemia in both sexes and the benign fibroadenoma of the mammary gland in females. As for the benign tumors that were found to be higher with treatment such as skin fibroma in males at HD, thyroid C-cell adenoma in females at HD, and adrenal pheochromocytoma in females at HD, these tumors are probably not drug related for the following reasons. 1) The occurrence of these tumors was not dose related 2) no malignant tumors of the same category were present or if present did not indicate a drug effect 3) the occurrence of these benign tumors was within the NTP historical control 4) according to our statistical review of the data, none of these tumors showed a significant level either in the individual study or the combined except for skin fibroma

which was significant in one study (R11282) but not in the other and as a result did not show statistically significant difference in the combined studies.

Carcinogenicity summary: two replicate studies in both rats and mice were conducted with a total of 60 animals/group/sex in each species. Drug was administered in food containing, 0.0, 0.03, 0.1 or 0.3% tomoxetine in mice and 0.0, 0.01, 0.03, or 0.1% tomoxetine in rats. These levels provided an estimated (since no food intake was measured) time-weighted average daily dose of 0, 34, 120 or 436 mg/kg in M mice and 0, 34, 124, 479 mg/kg in F mice. However, if a decrease in food consumption in these mice is assumed, these doses will be about 10% less as discussed earlier. In rats these levels provided time-weighted average daily doses of 0, 4, 13, or 43 mg/kg for M and 0, 5, 15, or 51 mg/kg for F. Body wt was decreased in M and F mice at the MD and HD. In rats there was a slight decrease in body wt in M at the HD and at all doses in F. A decrease in food consumption was seen at MD early in the study and at HD throughout the study in M rats and at all doses throughout the study in F. No measurement of food consumption was done in mice, but this was assumed to be decreased based on a subsequent study. No major changes in hematology or clinical chemistry were seen in mice. In rats, an increase in glucose levels was seen in M and an increase in BUN was seen in M at MD and HD and at all doses in F. Pathological changes were seen in the liver in mice and rats and these included nodular changes (M and F mice) and whole tissue alteration (F mice) and liver "lesions" in M rats at the HD and histologically, vacuolation in both M and F rats. Increased incidence of cataracts in M and F rats at HD. The incidence of fibroadenoma of the mammary gland in F rats appeared to decline with treatment and the incidence of mononuclear cell leukemia in M and F rats was also decreased with treatment. No clear increases in tumor incidences were seen in either mice or rats.

Carcinogenicity conclusions: from both the mouse and rat studies it does not appear that there is a major concern of tumor development in response to drug treatment. However, some concerns about the study conduct are expressed and specifically about the levels of exposure to the drug in these animals. As a result of the fixed levels of the drug substance in the feed together with the decrease in food consumption in rats and assumed decrease in food consumption in mice, it is of concern that levels of exposure were inconsistent throughout the studies. This was confirmed in the rat study where the calculated values of the drug substance that the rats were exposed to were higher at the beginning of the study in comparison to those at the end. In addition, no drug blood levels were measured to reflect the level of exposure in these animals and how they relate to the human exposure. The calculated doses at the HD in the rat study or the estimated levels in mice in comparison with proposed human maximum dose are shown below:

Species		Dose (mg/kg/day)	Dose (mg/m2/day)	Fold from human dose (using mg/m2/day values)
Rat	M	42.5	255	3.8
	F	51.3	307.8	4.6
Mouse	M	436	1308	19.6
	F	479	1437	21.6

*Mouse	M	401	1203	18
"corrected"	F	421.5	1264.6	19
Human		1.8	66.6	1

(*As discussed earlier, it is assumed that food consumption in these mice was lowered with drug treatment, since a later study [study # M00687] indicated this. If we consider the results obtained from this later study applicable to the 2-year carcinogenicity study, a decrease of 7% in food consumption for males and of 12% for females would be used to recalculate those levels of exposure ["corrected" mice values in the table]).

The following table was obtained from the sponsor's summary and compares plasma drug levels between animals and humans.

Comparison of Exposure Levels to Total Active Drug (Atomoxetine and 4-Hydroxyatomoxetine) in Animals and Humans

			Exposure Multiple for Unbound Total Active Drug[a]			
			C_{max}		AUC	
Species Dose	C_{max} ng/mL	AUC_{0-t} ng•hr/mL	EM	PM	EM	PM
Human[b]						
Adult Dog[d]						
NOAEL: 8 mg/kg/day	94 (1881)	514 (8979)	5.6 x	2.4 x	3.3 x	1.1 x
High dose: 16 mg/kg/day	194 (4318)	1148 (24196)	12 x	5.1 x	7.4 x	2.5 x
Young Dog[e]						
LOAEL: 4 mg/kg/day	73 (1362)	364 (5124)	4.4 x	1.9 x	2.4 x	0.8 x
High dose: 16 mg/kg/day	213 (4018)	1175 (18510)	13 x	5.5 x	7.6 x	2.6 x
Adult Rat[f]						
NOAEL: 0.01% in diet (7-8 mg/kg/day)	0.6 (4.8)	8.7 (72)	<0.1x	<0.1x	0.1 x	<0.1x
High dose: 0.1% in diet (69-75 mg/kg/day)	11 (58)	158 (908)	0.6 x	0.3 x	1.0 x	0.3 x
Young Rat[g]						
NOAEL[h]: 1 mg/kg/day	≤1.2 (≤4.9)	≤7.9 (≤33)	≤0.1x	<0.1x	≤0.1x	<0.1x
NOAEL[i]: 50 mg/kg/day	10 – 145 (66 – 498)	69 - 1228 (573 - 3725)	≤8.7 x	≤3.8 x	≤7.9 x	≤2.7 x
Adult Mouse[j]						
NOAEL: 0.1% in diet (150 mg/kg/day)	5.4 (26)	81 (384)	0.3 x	0.1 x	0.5 x	0.2 x
High dose: 0.4% in diet (600 mg/kg/day)	234 (1127)	2994 (14263)	14 x	6.1 x	19 x	6.5 x
Gravid Rabbit[k]						
NOAEL[l]: 100 mg/kg/day	64 (1169)	233 (3505)	3.8 x	1.7 x	1.5 x	0.5 x

Abbreviations: C_{max} = maximum observed plasma concentration; AUC_{0-t} = area under the plasma drug concentration versus time curve from time 0 to time of last concentration above quantifiable limits; EM = human CYP2D6 extensive metabolizer, PM = human CYP2D6 poor metabolizer, NOAEL = no-observed-adverse-effect level, LOAEL = lowest-adverse-effect level, M = male, F = female.

a Exposure multiple is the unbound atomoxetine + 4-hydroxyatomoxetine AUC_{0-t} in animals/unbound atomoxetine + 4-hydroxyatomoxetine $AUC_{0-24\ hr}$ in humans at steady state.

b Human plasma C_{max} and $AUC_{0-24\ hr}$ are based on data collected following multiple dosing in pediatric patients (atomoxetine; population analysis) and adult volunteers (4-hydroxyatomoxetine; clinical study B4Z-LC-LYAE) at the maximum recommended dose of 1.8 mg/kg/day (0.9 mg/kg BID).

c Unbound (and total) plasma atomoxetine levels. Unbound levels are based on in vitro protein binding data (ADME reports 5 and 48; 4-hydroxyatomoxetine binding to dog plasma was used to estimate unbound levels of 4-hydroxyatomoxetine in rabbit plasma).

d Plasma exposure for combined genders determined at 3 months (Toxicology Report 35); AUC, t=18 hr.

e Plasma exposure for combined genders determined at 1 month (Toxicology Report 44); AUC, t=24 hr.

f Plasma exposure for combined genders determined at 3 months (Toxicology Report 32); AUC, t=20 hr.

g Plasma exposure for combined genders determined on Postnatal Days 10 (highest value of range presented) and 84 (lowest value of range presented) (Toxicology Report 45); AUC, t=24 hr.

h NOAEL for general toxicity (Toxicology Report 45).

i NOAEL for neurobehavior (Toxicology Report 48) and reproductive performance (Toxicology Report 49).

j Plasma exposure for combined genders determined on Days 5 (high dose) and 90 (NOAEL) (Toxicology Report 34); AUC, t=20 hr.

k Plasma exposure determined in pregnant rabbits on Gestation Day 19 (Toxicology Report 42); AUC, t=24 hr.

l NOAEL for fetal development.

As can be seen in the table, AUC values at the HD (0.1%) in the rat carcinogenicity study are equal to or less than those in humans. In mice, AUC values at the HD (0.3%) in the carcinogenicity study were not represented in the table since AUC values at 0.1% and 0.4% were measured. It was evident from the toxicokinetic study that there was no dose proportionality in the increase in AUC values, therefore it would be difficult to accurately predict drug levels in response to treatment with 0.3% tomoxetine. The AUC values at the 0.1% and 0.4% bracketed the human value, however, the range between the two values is large and it is not clear where the values of the 0.3% dose fit in that range.

As is obvious from the previous discussion, the adequacy of the doses used is of major concern. Based on the decrease in body wt in both rats and mice, it is evident that an MTD was reached. However, if this decrease was due to poor palatability of the drug then this will indicate that the decrease in body wt was not due to drug toxicity but rather to the decrease in consumed food. As was seen from the rat study and from the later 3-month mice study (to measure the effect of the drug on food consumption in mice), there was a decrease in food consumption in both species with drug treatment. Therefore, it is possible that the decrease in food consumption, which was seen early in the study, is due to poor palatability and not due to drug toxicity. However, in other studies submitted in the NDA, where the drug was administered by gavage, decreases in body wt (toxrept 39, 45, and 53) and food consumption (toxrprt 45 and 53) were observed. Since drug administration by gavage also caused this decrease in body wt and food consumption, it

is possible that the decreases seen in the dietary carcinogenicity studies were due to drug toxicity and not palatability. The decrease in food consumption might be a pharmacological effect of the drug since treatment with the drug for up to 9 weeks in children and adolescents (human clinical trials) resulted in 14% of subjects reporting decrease in appetite compared to 6% in the placebo group.

Other observations that might be of further support that adequate exposure to the drug has been achieved is the higher incidence of death that was seen in one of the mice studies in M at the HD in comparison to controls. In addition, the observation of glomerulonephrosis in rats treated with the drug could also indicate that adequate exposure to the drug has been accomplished and kidney toxicity is caused by the drug.

In tox rept 53 the following two tables were provided by the sponsor to compare plasma levels of tomoxetine and its metabolites, from different types of treatments (i.e. gavage, dietary with fixed drug concentration, and dietary with targeted dose levels), to decreases in body wt and food consumption.

Body Weight Gain, Food Consumption, and Plasma Atomoxetine Exposure in Fischer 344 Rats During 1 Month of Oral Gavage Administration

LY139603 Oral Gavage Dose (mg/kg/day)	Body Weight Gain[a] (% Change from Control)		Food Consumption[a] (% Change from Control)		C_{max}[b] (mg/mL)		AUC[b] (ng•hr/mL)	
Gender	M	F	M	F	M	F	M	F
29	-	-	-	-	93	-	453	-
40	↓16*	↓10*	↓9*	↓5*	-	-	-	-
58	-	-	-	-	161	-	652	-
80	↓27*	↓28*	↓16*	↓13*	-	-	-	-
145	-	-	-	-	688	-	3094	-
160	↓39*	↓43*	↓23*	↓17*	-	-	-	-

Abbreviations: C_{max} = maximal plasma concentration of atomoxetine, AUC = area under the plasma atomoxetine concentration curve, F = female, M = male, - = not determined.

[a] Day 27 values from present study (R10901).

[b] Day 0 values from a single-dose pharmacokinetic study (——— 1998).

*p≤.05.

APPEARS THIS WAY
ON ORIGINAL

Body Weight Gain, Food Consumption, and Plasma Atomoxetine Exposure in Fischer 344 Rats During 1 Month of Dietary Exposure

LY139603 Dietary Dose (% in diet; estimated mg/kg/day)	Body Weight Gain (% Change from Control)		Food Consumption (% Change from Control)		C_{max} (mg/mL)		AUC (ng•hr/mL)	
Gender	M	F	M	F	M	F	M	F
0.01% 4 to 8 mg/kg/day	↓3[b] ↓2[c] ↓5[d]	↓7*[b] ↓6*[c] ↓10[d]	↑1[b] ↓2[c] ↓3[d]	↓5*[b] ↓3*[c] ↓1[d]	4.1-6.6[f]	3.4-5.4[f]	64-103[f]	80-89[f]
0.03% 13 to 24 mg/kg/day	↓6[b] ↓3[c] ↓10[d]	↓6[b] ↓2[c] ↓23*[d]	↓3[b] ↓3*[c] ↓6[d]	↓9*[b] ↓5*[c] ↓6*[d]	11-18[f]	13-16[f]	195-299[f]	236-246[f]
0.1% 42.5 to 75 mg/kg/day	↑7[a] ↓4[b] 0[c] ↓18*[d]	↓21*[a] ↓14*[b] ↓9*[c] ↓40*[d]	0[a] ↓3[b] ↓4*[c] ↓11*[d]	↓12*[a] ↓12*[b] ↓10*[c] ↓16*[d]	44-115[f]	24-52[f]	665-1199[f]	852-913[f]
40 mg/kg/day[i]	↓13*[e]	↓13*[e]	↓11*[e]	↓10*[e]	25-35[g]	17-25[g]	417-660[h]	315-411[h]
80 mg/kg/day[i]	↓21*[e]	↓32*[e]	↓15*[e]	↓16*[e]	38-55[g]	40-52[g]	838-1039[h]	873-987[h]
160 mg/kg/day[i]	↓36*[e]	↓51*[e]	↓21*[e]	↓24*[e]	89-129[g]	87-96[g]	1642-2425[h]	1741-1860[h]

Abbreviations: C_{max} = maximal plasma concentration of atomoxetine, AUC = area under the plasma atomoxetine concentration curve, F = female, M = male.

[a] Day 27 or 28 values are presented from : 1981.
[b] Day 27 or 28 values are presented from 1984.
[c] Day 27 or 28 values are presented from 1985.
[d] Day 27 or 28 values are presented from 998.
[e] Day 27 or 28 values are presented from — 1999.
[f] The range of pharmacokinetic values presented includes Days 5, 35, and 90 from (— 1998 (since only one time point was evaluated on Day 35 and since no substantive changes in plasma concentrations occurred during this period).
[g] Data generated on Days 5 and 35 from — 1999.
[h] Estimated AUC's based on 0:00 hr and 12:00 hr time points (— 1999).
[i] Dietary concentration of atomoxetine was adjusted to provide a fixed mg/kg dose (— 1999).
*p≤.05.

From these tables one can conclude that AUC values obtained from dietary studies with 0.1% tomoxetine (665-1199 ng.h/ml for M and 852-913 ng.h/ml for F) are within the range of values obtained from oral gavage doses of 58 and 145 mg/kg (652-3094 ng.h/ml for M). Using data obtained from a gavage study (tox rpt 53), the 80 mg/kg dose can be considered the MTD value since at this dose a decrease of 12% compared to control in body wt was seen in M and an 8% decrease was seen in F. The plasma levels from this gavage dose (80 mg/kg) were not measured. However, from the table summarizing the gavage studies, it could be estimated to be more than 652 ng.h/ml but less than 3094 ng.h/ml (values obtained from 58 and 145 mg/kg). The value is more likely to be closer to the lower value than to the upper one (80 is closer to 58 than to 145. Therefore, under the current circumstances, one can conclude that administering the drug by gavage at an MTD dose of 80 mg/kg/day might not result in a substantial difference in plasma levels

compared to what might be obtained from a 0.1% tomoxetine dose administered in the diet.

The reviewer has some reservations about the conduct of the studies, however, the findings did not indicate any serious neoplastic change. Considering the decrease in body wt seen in both species as a toxic effect of the drug and the increase in mortality in mice and the drug related glomerulonephrosis in rats, an MTD could be considered as fulfilled. Therefore, it could be concluded that the drug is not a carcinogen.

Recommendations for further analysis: no further analysis is required.

Labeling Recommendations: from studies in rats and mice treated with atomoxetine at concentrations approximately equal to 47 mg/kg (rat) and 458 mg/kg (mice) for two years, atomoxetine was not carcinogenic. The doses used in rats are approximately 4 times the maximum recommended human dose based on mg/m^2 exposure and 1.4 times (EM) and 0.15 times (PM) the maximum recommended human dose based on AUC values. The doses used in mice are approximately 21 times the maximum recommended human dose based on mg/m^2 exposure.

Addendum/appendix listing:
CAC report:

Executive CAC
Date of Meeting - May 14, 2002

Committee: Joseph Contrera, Ph.D., HFD-901, Acting Chair
Abigail Jacobs, Ph.D., HFD-540, Alternate Member
Al DeFelice, Ph.D., HFD-110, Alternate Member
Barry Rosloff, Ph.D., HFD 120, Team Leader
Ikram M. Elayan, Ph.D., HFD 120, Presenting Reviewer

Author of Draft: Ikram M. Elayan

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

NDA #: 21411
Drug Name: atomoxetine hydrochloride (Straterra).
Sponsor: Eli Lilly

Background: atomoxetine hydrochloride is a norepinephrine reuptake inhibitor intended for the treatment of ADHD in both children and adults. The compound was not genotoxic in Ames test, in *in vitro* chromosomal aberrations in CHO cells, and in *in vivo* micronucleus in ICR mice.

Rat Carcinogenicity Study: two replicate studies each with 30 rats/sex/group were conducted two weeks apart. Tomoxetine at concentrations of 0.0, 0.01, 0.03, and 0.1% was administered orally in diet for two years. These levels were kept constant and were not adjusted for changes in body wt. These levels represented time-weighted average daily doses of 4&5 mg/kg at LD, 13&15 mg/kg at MD, and 43&51 mg/kg at HD in M and F, respectively. Doses used in this study were based on findings from previous 3-month and 1-year toxicity studies at concentrations up to 0.1% in which decreases in body weight of 10-17% compared to control were reported. The results of this study indicated a decrease in body weight in M at HD (5% compared to control) and F at HD (15%), MD (7%) and LD (3%) at the end of the study. Moderate (M and F) to severe (M) progressive glomerulonephrosis was observed with treatment. In light of these findings, an MTD was considered to have been reached. A decrease in food consumption was seen with treatment in both M and F. This decrease was also seen in studies where the drug was administered by gavage suggesting that the decrease in food consumption was an effect of the drug rather than due to poor palatability. There was no obvious tumor development in response to treatment.

Mouse Carcinogenicity Study: two replicate studies each with 30 mice/sex/group were conducted two weeks apart. Drug was administered orally in diet at fixed concentrations of 0.0, 0.03, 0.1, and 0.3%. Doses were estimated (from body weights of animals on the study and food consumption of the historical control) to be 34 mg/kg at the LD, 120&124 mg/kg at the MD, and (corrected for the decrease in food consumption observed in a later study) 401&422 mg/kg at HD in M and F, respectively. Doses used in this study were based on doses used in a 3-month toxicity study (0.025, 0.1, and 0.4% tomoxetine was given orally in diet) where decreases in body wt of 13% compared to control in M and 9% in F were reported. In the carcinogenicity study death occurred earlier in M at the HD in comparison to the control group. Decreases in body wt at MD (7% compared to control) and HD (19%) in M and MD (10%) and HD (32%) in F were reported at the end of the study. Based on these findings an MTD is considered to have been reached. There was no obvious tumor development in response to treatment.

Executive CAC Recommendations and Conclusions:
The committee concurred that the rat study was adequate and an MTD was reached based on the decrease in body weight, which was considered a drug effect since this decrease was also observed in gavage studies. The committee also concurred that there were no significant tumor findings in response to treatment.
An MTD was also considered to have been reached in the mouse study based on the increase in mortality rate in male mice at the high dose and the decrease in body weight. The committee concurred that the study was adequate and that no significant tumor findings were observed in response to treatment.

Joseph Contrera, Ph.D.
Acting Chair, Executive CAC

cc:\
/Division File, HFD 120
/Barry Rosloff, HFD-120
/Ikram Elayan, HFD-120
/Anna Marie Homonnay, HFD-120
/ASeifried, HFD024

VII. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLGY:

Study title: an eight-month fertility, perinatal, and postnatal study, including behavioral and reproductive assessment of the F1 generation, in CD rats given diets containing tomoxetine (LY 139603)

Key study findings: slightly higher incidence of early resorptions, some delay in postnatal physical development in the progeny, decreased female fetal wt, and a hint of incomplete skeletal ossification

Study no: studies R07987, R08087, R08187, and R13787
Volume #, and page #: toxicology rept 27, volumes 51-52
Conducting laboratory and location: Department GL796
Lilly Research Laboratories
Division of Eli Lilly and company
Greenfield, Indiana 46140

Date of study initiation: Study R07987, May 4 1987 to September 2, 1987
Study R08087, June 29 1987 to September 14, 1987
Study R08187, July 13, 1987 to September 3, 1987
Study R13787, September 1, 1987 to January 7, 1988

GLP compliance: yes
QA reports: Yes (X) No ()
Drug, lot #, radiolabeled, and % purity: tomoxetine, lot #174MH6, 99.6%
Formulation/vehicle: dietary/mash feed (—— Rodent Chow ——). The diets were prepared every two weeks. The drug appeared to be homogenous in the diet (only the 0.025% was tested) and stable for 5 weeks.

Methods:

Species/strain: rats/CD

Doses employed: tomoxetine dietary at concentrations of 0.0, 0.01, 0.03, and 0.06% which produced a time-weighted average of 0, 7, 20 and 40 mg/kg/day for males and 0, 7, 20, and 41 mg/kg/day for females.

Route of administration: orally/diet

Study design: Study R07987 males treated with tomoxetine for 10 weeks prior to mating and throughout two mating trials. At approximately 15-17 weeks of age they were mated with females in the studies below.

Study R08087 females of the delivery component, treated with tomoxetine for two weeks prior to mating and throughout mating, gestation, and lactation.

Study R08187 females of the teratology component were treated for two weeks prior to mating and throughout mating and gestation and were killed on gestation day 20 for assessment of reproductive and fetal parameters.

Study R13787, F1 generation study, weanling rats (one pup/sex/litter) from study R08087 maintained on control diets after postpartum day 21. Behavioral tests were performed at age of 30-60 days. Rats from the corresponding parental treatment groups were mated at approximately 15 weeks of age (females were allowed to deliver and rear their F2 progeny). At approximately 22 weeks of age the surviving F1 parental animals were killed and gross necropsy was performed and reproductive tissues were collected for histopathological evaluation.

Number/sex/group: F0 Generation: Males (study R07987) – 20/group
Females (study R08087) – 20/group
Females (study R08187) – 20/group
F1 Generation (Study R13787): 16, 19, 19, and 19 rat/sex in the 0, 0.01, 0.03, and 0.06% treatment groups, respectively.

Parameters and endpoints evaluated:

Study R07987 males, body weights and clinical signs were recorded during the growth and reproduction periods.

Study R08087 females of the delivery component, body wt was recorded weekly during cohabitation periods until mating, on postmating days 0, 7, 14, and 21, and on postpartum days 1, 7, 14, and 21. Food consumption was recorded on postmating days 0, 7, 14, and 21, and on postpartum days 0, 7, 10, and 14. Reproduction measurements such as precoital periods, gestation length, and number of live and dead progeny on the day of delivery. Progeny measurements for this group included: counting, sex determination, weighing the progeny on postpartum days 1, 7, and 14 as litters and on day 21 individual pups were weighed. On postpartum days 10-12 and 15-17 each pup was examined for incisor eruption and eye opening, respectively.

Study R08187 females of the teratology component: body wt was recorded weekly during the cohabitation period and on postmating days 0, 7, 14, and 20. Food consumption was recorded on postmating days 0, 7, 14, and 20. Reproduction measurements were recorded which included the following parameters: wt of uterus and ovaries, number of corpora lutea in each ovary, the number and distribution of implantations, live and dead fetuses, and resorptions. All females assigned to this group were given gross internal examination and

unusual findings were confirmed by a veterinary pathologist. Fetal measurements included external examination of individual fetuses for anatomical anomalies and sex determination. One half of the gestation day 20 fetuses from each litter were fixed in Bouin's solution for visceral examination and the remaining fetuses were used for skeletal examination.

Study R13787 F1 generation: body wt and food consumption during the growth period for both males and females. F1 females were weighed weekly during the cohabitation periods until mating was confirmed, on posmating days 0, 7, 14, and 21, on postpartum day 1, and at termination. Food consumption was collected on postmating days 0, 7, 14, and 21 for delivering females. Behavioral tests (one-hour activity levels in automated Figure-8 mazes and the auditory startle habituation test) were conducted on all animals. For the one-hour activity test, each animal (at ages 30 $\pm$ 1 and 60 $\pm$ 2 days) was placed individually in a maze, and the number of photobeam breaks was recorded cumulatively by computer during four, sequential 15-minute intervals. For the auditory startle habituation, animals (age 55 $\pm$ 2 days) were exposed to a test session that consisted of a 5-minute acclimation period in the test chamber at a background noise level of 70 $\pm$ 3 dBA. Each animal was then presented a 50-millisecond burst of white noise at 120 $\pm$ 2 dBA, and response data were recorded for a period of 100 milliseconds following noise onset. A total of 50 noise burst presentations was given for each animal at fixed intervals of eight seconds. Computer-recorded data for each animal on each trial included the peak amplitude of the startle response, and the latency from noise onset to the animal's peak response. For each animal, data were summarized into five consecutive 10-trial mean values (trial Blocks 1-5).

At approximately 15 weeks of age, rats from corresponding parental treatment groups were mated and the females were allowed to deliver and rear their F2 progeny. Mating and fertility indexes were assessed. All animals were necropsied and a systemic gross examination of each animal's general physical condition, body orifices, external and internal organs and tissues was performed. The following organs and tissues were collected for histopathological examination: ovary, uterus, vagina, testis, epididymis, seminal vesical, prostate, and tissues containing gross lesions. Histological examinations were done for the control and HD groups.

Results:

Mortality: none of the parental animals in F0 or F1 generation died.

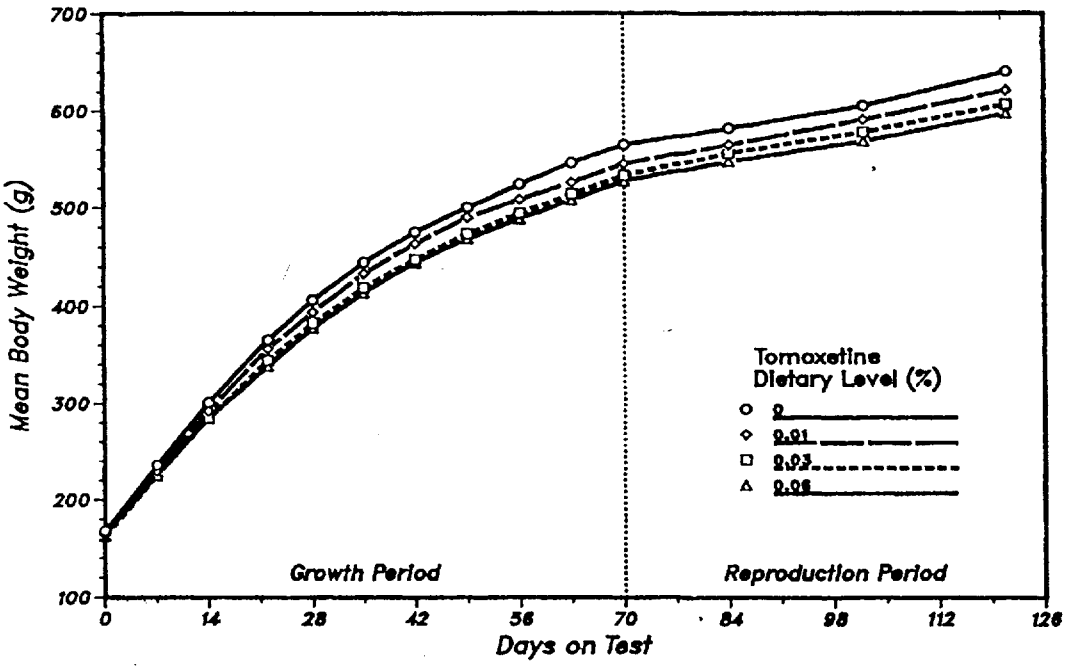
Clinical signs: F0: alopecia (females 31%, 37%, 40%, and 37% of animals in control, LD, MD, and HD groups, respectively), chromodacryorrhea (males 5%, 16%, 10%, and 21% of animals in control, LD, MD, and HD), and "injury" (males 10% of animals at HD and 0 in all other groups) were reported.

F1: alopecia (males 0, 5%, 25%, and 16% in control, LD, MD, and HD group respectively while females 25%, 26%, 21%, and 42% of animals in control, LD, MD, and HD groups, respectively), chromodacryorrhea (males 6%, 11%, 5%, and 16% in control, LD, MD, and HD, respectively), incisor overgrowth (males 6%, 21%, 21%, and 26% in control, LD, MD, and HD, respectively), tail red or scaly (males 0, 5%, 5%, and 10% in

control, LD, MD, and HD) were reported. A mass was seen in one of the F1 females of the 0.06% group on test days 97-129. The mass regressed after parturition, histopathologically the mass was diagnosed as mammary hyperplasia.

Body weight: F0 males showed a decrease in body wt at all doses. However, only decreases at MD (6% compared to control, from day 22-42) and HD (7%, from day 22-70) were statistically significant. Decreases in body wt gain were also seen (~8% compared to control) at MD and (~11%) HD and were statistically significant up to day 42 in the MD and throughout the study at HD.

FIGURE 5. MEAN BODY WEIGHTS OF MALE RATS GIVEN DIETS CONTAINING TOMOXETINE. FERTILITY STUDY R07987, F_0 MALE COMPONENT.



F0 females of the delivery component: decreases in body wt occurred at MD and HD (~5%) in the premating period, however, they were not statistically significant at any time point. During the 21-day gestation period, decreases were seen at all doses however they were statistically significant only at the HD (6% decrease compared to control) up to day 14. Decreases in body wt were also seen in the postpartum period at all doses, but were statistically significant only at the HD (7% decrease compared to control) and only on days 14 and 21. At termination body wt was decreased with statistical significance only at the HD (7% compared to control) even though the decrease was also observed at the MD. Decreases in wt gain in this group were seen at HD (44%) between premating days 1-7. See the following figures provided by the sponsor.

FIGURE 6. MEAN BODY WEIGHTS OF FEMALE RATS GIVEN DIETS CONTAINING TOMOXETINE. FERTILITY STUDY R08087, F_0 DELIVERY COMPONENT.

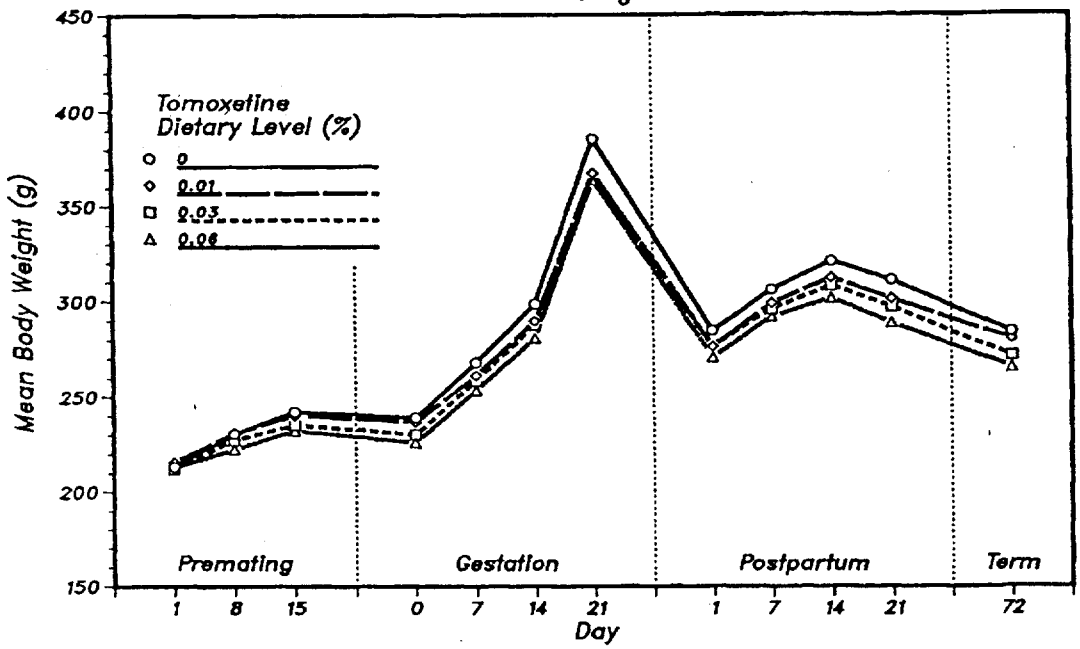
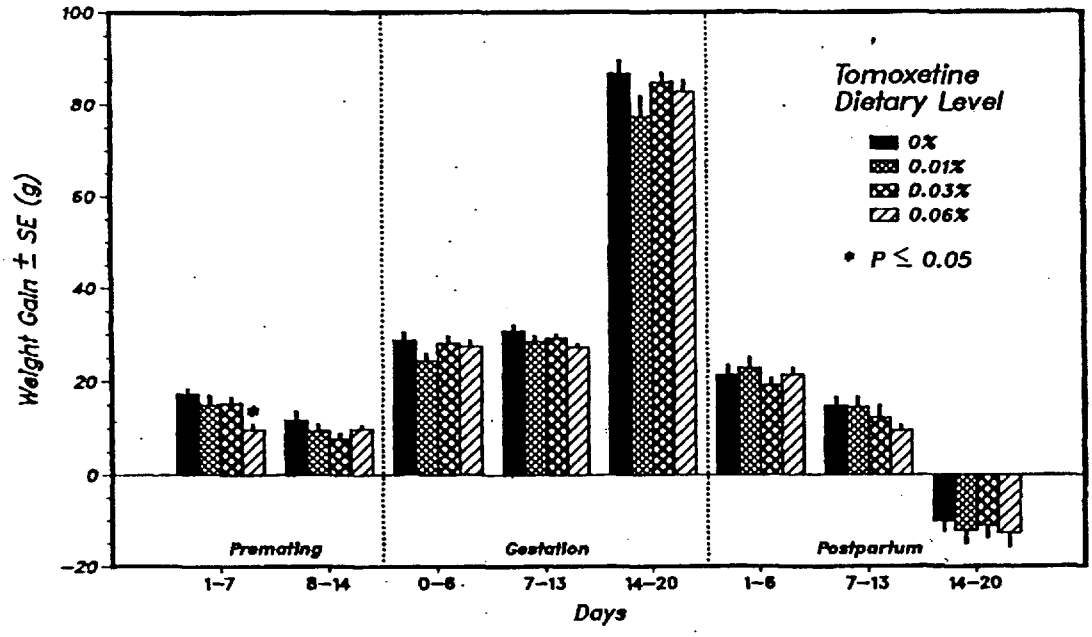


FIGURE 10. MEAN BODY WEIGHT GAIN BY WEIGH PERIOD FOR FEMALE RATS GIVEN DIETS CONTAINING TOMOXETINE. FERTILITY STUDY R08087, F_0 DELIVERY COMPONENT.



F0 females of the teratology component: decreases in body wt during the premating period were not significant. Decreases during the gestation period were seen at the MD (~8% compared to control, days 7, 14 and 20) and the HD (~6% compared to control, days 14 and 20). Decreases in body wt gain were observed in this group during the premating period at HD (40%) and MD (25%, not statistically significant) between days 1-7. During the gestation period body wt gain was decreased (29%) in MD between gestation day 0-6 and at HD (17%) between gestation day 7-13. During the whole gestation period the decreases were 15% at MD and 11% at HD. Net wt gain (body wt gain minus uterine weight) was decreased by 24% at MD and by 17% at HD compared to control in this group during the gestation period. See the following figures.

FIGURE 7. MEAN BODY WEIGHTS OF FEMALE RATS GIVEN DIETS CONTAINING TOMOXETINE. FERTILITY STUDY R08187, F_0 TERATOLOGY COMPONENT.

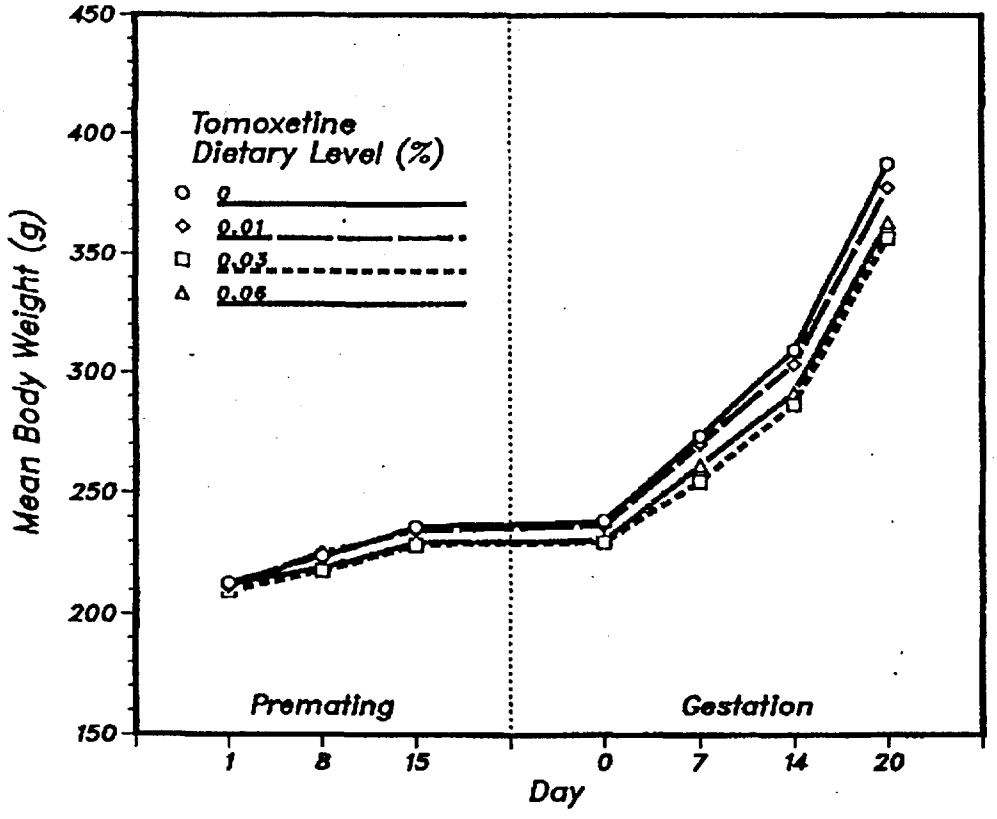
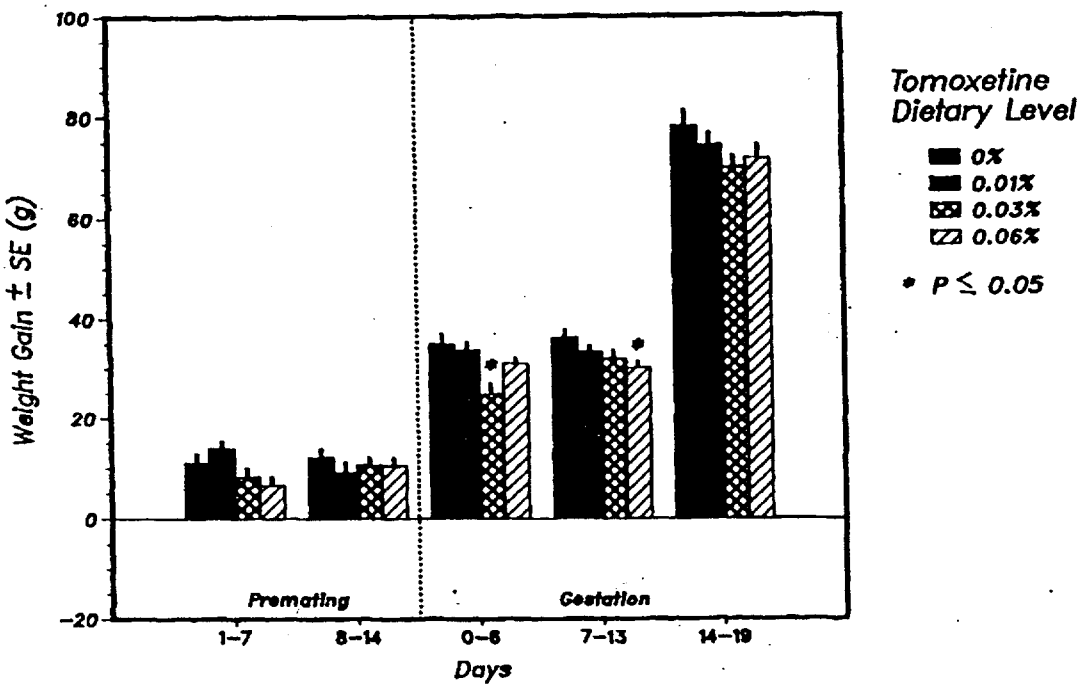


FIGURE 11. MEAN BODY WEIGHT GAIN BY WEIGH PERIOD FOR FEMALE RATS GIVEN DIETS CONTAINING TOMOXETINE. FERTILITY STUDY R08187, F_0 TERATOLOGY COMPONENT.



F1 generation, males: there were no significant differences in body wt between control and treated groups at any time (growth or reproduction period).
F1 generation, females: there were no significant differences in body wt between control and treated groups at anytime during growth, gestation, and post partum.

Food consumption: F0 males: decreases in food consumption were observed at MD (11% compared to control) and the HD (14%) from day 7 to the end of the 70-day growth period.

F0 females of the delivery component: food consumption was depressed at the MD (11% compared to control) and HD (12-16%) during the premating days 1-14. This decrease was statistically significant. A statistically significant decrease was only observed at the HD (7%) during gestation days 7-13.

F0 females of the teratology component: food consumption was decreased in a statistically significant manner at the MD (11% compared to control) and HD (13%) during premating days 1-7. Decreases were seen at the MD and HD (~7% in both) almost throughout the gestational period (0-19 at MD and 7-19 at HD) and at the LD (7%) during days 14-19.

F1 generation: for both males and females there was no significant difference in food consumption between treated and control groups.

Toxicokinetics: none.

For fertility studies:

In-life observations:

Mating performance and fertility, F0 generation (delivery and teratology component): there was no drug effect on mating index (proportion of mating pairs that mated relative to the number of mating pairs cohabitated; expelled and retained copulatory plugs, vaginal sperm, and pregnancy were used as evidence of mating) or fertility index (the proportion of fertile mating pairs relative to the number of mating pairs that mated, pregnancy was used as evidence of fertility) in both the teratology and delivery components. There was no drug effect on precoital period length in both the delivery and teratology component.

Reproduction parameters, F0 delivery component: there was no drug effect on gestation length, litter size, or live birth index.

For the teratology component the number of early resorptions at the HD was higher than the control (the mean was 1.4 for HD vs. 0.8 for control and when expressed as % the values were 9.92% for HD vs. 5.52% for control). The sponsor stated that the value was not statistically significant and was within the historical control range (range for the number resorptions was and for % was 1.3%-19.1%).

Terminal and necroscopic evaluations:

F0, females of the teratology component: gross findings on females of the teratology component did not indicate any drug effect.

Embryofetal development evaluations:

In-life observations:

Progeny measurements for F0 delivery component: there was no drug effect on survival index (post natal days 1, 7, 14, 21), body wt, body wt gains or sex ratio in the progeny. Some effects on "morphological development" as described by the sponsor, which may be more appropriately described as physical development (incisor eruption and eye opening), were observed at MD and HD. For example, on day 10 there was a 67% decrease from control in the % of rats with erupted incisors at the MD dose and a 24% decrease at HD. On day 12 there was a 16% decrease at MD and a 23% at HD. In addition, the levels of open eyes appeared to be decreased in response to treatment. For example, on day 15 the percent positive per litter for open eyes in all of the treatment groups was 0 and for the control it was 2.3. These values were lower than the control at all treatment doses on days 16 and 17 even though they were not dose dependent (values were 63%, 24%, and 50% lower than the control on day 16, and 39%, 34%, and 22% lower than control on day 17, for the LD, MD, and HD respectively). The sponsor did not endorse these changes and stated that they were not statistically significant.

TABLE 27.

MORPHOLOGICAL DEVELOPMENT SUMMARY FOR LITTERS FROM RATS GIVEN DIETS CONTAINING TOMOXETINE. FERTILITY STUDY R08087, F0 DELIVERY COMPONENT.

TOMOXETINE DIETARY LEVEL (%)	STATISTIC	DAY 10 ERUPTED INCISORS(a)	DAY 11 ERUPTED INCISORS	DAY 12 ERUPTED INCISORS	DAY 15 OPEN EYES(b)	DAY 16 OPEN EYES	DAY 17 OPEN EYES
0	MEAN	7.8	29.7	65.6	2.3	7.8	35.9
	STD	11.1	24.5	24.8	6.8	12.0	25.8
	STDERR	2.8	6.1	6.2	1.7	3.0	6.4
	N	16	16	16	16	16	16
0.01	MEAN	8.1	27.2	54.1	0.0	2.9	21.9
	STD	18.3	30.1	34.5	0.0	5.7	19.8
	STDERR	4.2	6.9	7.9	0.0	1.3	4.5
	N	19	19	19	19	19	19
0.03	MEAN	2.6	25.0	55.3	0.0	5.9	23.7
	STD	6.7	24.3	28.4	0.0	9.7	18.6
	STDERR	1.5	5.6	6.5	0.0	2.2	4.3
	N	19	19	19	19	19	19
0.06	MEAN	5.9	29.0	50.8	0.0	3.9	27.9
	STD	16.3	26.6	31.4	0.0	7.3	23.9
	STDERR	3.7	6.1	7.2	0.0	1.7	5.5
	N	19	19	19	19	19	19

NOTE: REPEATED MEASURES ANALYSIS OF VARIANCE, NO STATISTICALLY SIGNIFICANT MAIN EFFECT OF TREATMENT (P <= 0.05).

a - ALL FOUR INCISORS ERUPTED THROUGH GUM; PERCENT POSITIVE PER LITTER.
b - EYELIDS COMPLETELY SEPARATED; PERCENT POSITIVE PER LITTER.

Fetal parameters for the teratology component: body wt of female fetuses of animals treated with HD were 7% lower than those of control group. There was no significant difference in sex ratio between treated and control groups. In the external examination few changes were seen that did not appear to be drug related since they were seen at the LD only (additional hind limb, additional urogenital tubercle). Hematoma was reported for two fetuses from two litters at the HD, one fetus from one litter at the MD and none in the control or the LD group.

Terminal and necropsic evaluations: visceral examination of fetuses did not indicate a drug effect. Various anomalies (renal cavitation and ureter dilation) were seen in both control and treated groups. As for the skeletal examination some incomplete ossification was observed in several bones. The incidence of these anomalies was higher in some of the treatment groups in comparison to controls, however, they did not reflect a dose response effect. For example, incomplete ossification of the parietal bone was seen in 0 fetuses in control, 7 fetuses from 4 litters at the LD, 1 fetus at the MD, and 8 fetuses of 3 litters at the HD. Incomplete ossification of the interparietal was seen in 1 fetus in the control, in 7 fetuses of 4 litters at the LD, 1 fetus at the MD, and 5 fetuses of 3 litters at the HD. Incomplete ossification of the occipital bone was seen in 1 fetus in the control (same fetus with interparietal bone incomplete ossification), 3 fetuses of the same litter at

the LD, 1 fetus at the MD, and 3 fetuses of the same litter at the HD. Incomplete ossification of the sternebrae was seen in 1 fetus in the control, 2 fetuses of the same litter at the LD, 1 fetus at the MD, and 3 fetuses of 2 litters at the HD. Incomplete ossification of vertebral arch was seen in 1 fetus in the control group, 2 fetuses of two litters at the LD, 2 fetuses of 2 litters at the MD, and 7 fetuses of 4 litters at the HD. Incomplete ossification of pubis was not seen in the control group, 2 fetuses of the same litter at the LD, 1 fetus at the MD, and 4 fetuses of 3 litters at the HD. There was one fetus at the MD dose that had several of these anomalies. At the LD and the HD, generally the affected animals (incomplete ossification) experienced this observation in more than one bone. In addition incomplete fusion of the sternal bars was seen in 1 fetus in the control group, 1 fetus in the LD, 0 at the MD and 4 fetuses of 4 litters at the HD.

TABLE 32. DEVELOPMENTAL ANOMALIES IN FETUSES OF FEMALE RATS GIVEN DIETS CONTAINING TOMOXETINE. FERTILITY STUDY R08187, TERATOLOGY COMPONENT.

	Dose Level (%)			
	0	0.01	0.03	0.06
Examination Type	Fetuses (Litters[a]) Examined			
External	267 (20)	255 (19)	232 (18)	264 (20)
Visceral	138 (20)	131 (19)	119 (18)	135 (20)
Skeletal	129 (20)	124 (19)	113 (18)	129 (20)
External Anomalies	Fetuses (Litters[a]) Affected			
Additional hind limbs	0 (0)	1 (1)[b]	0 (0)	0 (0)
Additional tubercle (urogenital)	0 (0)	1 (1)[b]	0 (0)	0 (0)
Curved tail	0 (0)	0 (0)	0 (0)	1 (1)[c]
Edema	1 (1)[d]	0 (0)	0 (0)	1 (1)[c]
Hematoma	0 (0)	0 (0)	1 (1)	2 (2)
Visceral Anomalies				
Microphthalmia	0 (0)	1 (1)	0 (0)	0 (0)
Misshapen heart	1 (1)[d]	1 (1)e	0 (0)	0 (0)
Situs inversus (heart)	0 (0)	1 (1)e	0 (0)	0 (0)
Renal cavitation	11 (5)	4 (4)	5 (5)	6 (5)
Ureter dilatation	5 (4)	1 (1)	2 (2)	5 (3)
Dark adrenal gland	2 (2)	0 (0)	1 (1)	0 (0)
Inguinal hernia	0 (0)	1 (1)	0 (0)	0 (0)

TABLE 32. (Continued) TOMOXETINE, STUDY RD8187.

	Dose Level (%)			
	0	0.01	0.03	0.06
Skeletal Anomalies	Fetuses (Litters[a]) Affected			
Incomplete ossification of nasal bone	0 (0)	0 (0)	1 (1)f	0 (0)
Incomplete ossification of frontal bone	0 (0)	1 (1)	1 (1)f	1 (1)
Incomplete ossification of parietal bone	0 (0)	7 (4)	1 (1)f	8 (3)
Incomplete ossification of interparietal bone	1 (1)	7 (4)	1 (1)f	5 (3)
Incomplete ossification of occipital bone	1 (1)	3 (1)	1 (1)f	3 (1)
Cervical rib	0 (0)	0 (0)	1 (1)	1 (1)
Incomplete ossification of rib	0 (0)	1 (1)	0 (0)	2 (1)
Rudimentary rib (T13, T14, L1)	9 (5)	10 (7)	4 (4)	6 (3)
Short rib (T1)	0 (0)	0 (0)	1 (1)f	0 (0)
Wavy rib	1 (1)	3 (3)	0 (0)	3 (2)
Bifid rib	0 (0)	0 (0)	1 (1)	0 (0)
Incomplete ossification of sternebrae	1 (1)	2 (1)	1 (1)f	3 (2)
Misalignment of sternal bars	1 (1)	1 (1)	3 (3)	2 (2)
Incomplete fusion of sternal bars	1 (1)	1 (1)	0 (0)	4 (4)
Incomplete ossification of vertebrae	0 (0)	0 (0)	1 (1)f	0 (0)
Vertebrae absent (one lumbar)	0 (0)	1 (1)	0 (0)	0 (0)
Extra vertebrae (T14)	0 (0)	1 (1)	0 (0)	0 (0)
Incomplete ossification of vertebral arch	1 (1)	2 (2)	2 (2)	7 (4)
Incomplete ossification of vertebral centra	0 (0)	0 (0)	1 (1)f	0 (0)
Bipartite vertebral centrum	1 (1)	0 (0)	1 (1)f	2 (2)
Incomplete ossification of ischium	0 (0)	1 (1)	1 (1)f	2 (2)
Incomplete ossification of pubis	0 (0)	2 (1)	1 (1)f	4 (3)
Incomplete ossification of metacarpals	0 (0)	1 (1)	0 (0)	1 (1)
Incomplete ossification of metatarsals	0 (0)	0 (0)	1 (1)f	0 (0)

Note: One dead fetus from the low dose group had edema.

[a] Litters with live fetuses

b,c,d,e,f, Same fetus

According to the sponsor, these were similar to incidences seen in other teratology studies (provided in appendix F). Examining these data it was apparent that these incidences when compared to the current study represented as % of the total number of fetuses examined would be less than what is observed in the current study. For example the rate of incomplete ossification of the parietal bone in the current study was 6% (#of fetuses with this anomaly/total number of fetuses examined) and the cumulative rate from historical data was 1.19% (ranged from 0-3%). Similarly, the incomplete ossification of the interparietal bone in this study was 6% at LD and 4% at HD while in the cumulative historical control data it was 0.76% (ranged from 0-3%), incomplete fusion of the sternal bars in this study was 3% while in the historical control data it was 0.43% (ranged from 0-1.4%), and incomplete ossification of the vertebral arch in this study was 5% at HD and in historical control date it was 1.03% (ranged from 0-2.7%). Therefore, the rate at which these anomalies were occurring in treated animals in the current study was higher than in the historical control, however, the effect seen in this study was not dose dependent.

Peri-postnatal development studies:

In –life observations:

Postweaning behavioral assessments, F1 generation: no apparent drug effect on Figure-8 maze activity test of F1 animals (both M&F) on age days 30 and 60. There was